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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/336,103	06/18/99	DOWNS K	960296.95912

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EXAMINER	
WILSON, M	
ART UNIT	**PAPER NUMBER**
1633	11

DATE MAILED: 09/12/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/336,103	DOWNS, KAREN M.	
	Examiner	Art Unit	
	Michael Wilson	1633	

-- The MAILING DATE of this communication appears on the cover she t with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 June 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20 and 24-27* is/are pending in the application.

4a) Of the above claim(s) *1-13,15,16 and 18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14,17,19,20 and 24-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Continued Prosecution Application

The request filed on 6-19-01, paper number 9, for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/336103 is acceptable and a CPA has been established. An action on the CPA follows.

Election/Restriction

Applicants have elected to focus on a different restriction group. Applicant's election without traverse of Group III in Paper No. 10 is acknowledged. Claims 1-13, 15, 16 and 18 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Claims 21-23 have been canceled. Claims 24-27 have been added. Claims 14, 17, 19, 20 and 24-27 are under consideration as they relate to a method of observing vasculogenesis in culture. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Double Patenting

Claims 24-27 are objected to under 37 CFR 1.75 as being a substantial duplicate of claims 14, 17, 19 and 20. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Specification

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: A method of observing vasculogenesis *in vitro* using cultured allantois.

The following articles cannot be found: Downs et al., Development, submitted 1999 (page 2, line 6, and elsewhere throughout the specification) and Temkin et al., 1998, Development (page 25, line 17). Clarification is required.

The first line of the specification should state that 08/838384 has been abandoned. Since 08/838384, 60/015,066 and 60/118,764 were not and will not be readily available to the public, the subject matter of these applications cannot be incorporated by reference as stated in the first paragraph of the specification. Deletion of the sentence on page 1, line 5 is required. If applicants wish to incorporate essential subject matter disclosed in 08/838384, 60/015,066 and 60/118,764 that is not disclosed in the instant application, such incorporation should be done by amendment and not merely incorporation "by reference."

Claim Objections

Claim 27 is objected to because of the following informalities: the phrase "gene product" should be changed to "protein" to be more clear as proteins are the only "products" of genes. Appropriate correction is required.

Claim Rejections - 35 USC § 112

1. Claims 14, 17, 19, 20 and 24-27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for 1) a method of determining the fate of allantois tissue in an embryo comprising: a) isolating allantoic tissue from a transgenic mouse whose genome comprises a nucleic acid sequence encoding a marker gene operably linked to a promoter, wherein said allantoic tissue functionally expresses said marker protein to detectable levels, b) transplanting the allantoic tissue functionally expressing the marker protein into a recipient embryo that does not express said marker protein and c) observing the fate of the allantoic tissue functionally expressing the marker protein in the recipient embryo, 2) a method of determining whether a compound effects vascularization of allantois tissue *in vitro* comprising: a) isolating allantoic tissue, b) culturing said allantoic tissue *in vitro*, c) treating the allantoic tissue with a compound; c) observing the vascularization of the allantoic tissue treated with the compound, wherein an alteration in the vascularization of the allantoic tissue treated with the compound as compared to an allantoic tissue not treated with the compound indicates that the compound effects vascularization of allantoic tissue and 3) a method of observing vascularization of allantois tissue *in vitro* comprising: a) isolating allantoic tissue comprising a nucleic acid sequence encoding a marker protein operably linked to a promoter, wherein said allantoic tissue functionally expresses said marker protein to detectable levels, b) culturing said allantoic tissue *in vitro,* and c) observing the vascularization of the allantoic tissue does not reasonably provide enablement for performing the method as broadly claimed. The specification does not enable any person skilled

in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The specification teaches isolating allantois explants from transgenic mice expressing marker proteins (page 42, line 8) and isolating allantoises transfected with a vector encoding a marker protein *in vitro* (page 79, line 23). The isolated allantoises were transplanted into non-transgenic embryos and their growth, movement, development and vascularization were observed in the embryos (page 64, line 6 for example). In addition, the vascularization of allantoises transfected *in vitro* and cultured under different conditions was observed *in vitro* (page 80, line 18 through page 81, line 6). Thus, various methods are disclosed in the specification.

The specification does not enable observing vasculogenesis as broadly claimed. The essential steps required to perform the methods encompassed by the claims vary and depend upon what aspect of vasculogenesis is being observed. For example, the specification does not teach how to observe growth, movement, development or vascularization of donor allantoic tissue in recipient embryos where the donor tissue does not functionally express a marker protein to detectable levels. If the donor and recipient cells are the same, the method cannot be performed because the donor cells cannot be distinguished from the recipient cells. The specification does not teach detecting donor cells using any protein other than marker proteins. If applicants intend the claims to be directed towards observing the fate of an allantoic cell within an embryo, the claims should be limited to allantoic tissue comprising a nucleic acid sequence encoding a marker

gene operably linked to a promoter, wherein said allantoic tissue functionally expresses said marker protein to detectable levels.

If the claims require transplanting donor tissue into recipient embryos, the claims should be limited to histocompatible, allogeneic or syngeneic transplantation. The specification does not provide adequate guidance for one of skill in the art at the time of filing to transplant a histoincompatible or xenogeneic transplant in the method claimed which would result in an immune response against the donor tissue by the host immune system. Functional transplantation requires the host be histocompatible so as to avoid an attack by the host immune response. Therefore, for the method claimed to be of use, the effect of an expressed protein on vasculogenesis can only be observed if the host is histocompatible, allogeneic or syngeneic.

Claims 17, 19, 20 and 25-27 require observing the effect of a compound on vasculogenesis. Such a method requires comparing the effect of the compound on vasculogenesis to a control and interpretation of such a comparison. The specification does not teach applying an exogenous protein or drug to an allantois, observing their effects on vasculogenesis or how to determine if the compound has an effect on vasculogenesis. While such an assay can be imagined, such a method would require comparing the vascularization of an allantois contacted with a compound to the vascularization of an allantois not contacted with said compound, wherein an alteration in the vascularization of the allantois contacted with said compound as compared to the vascularization of the allantois not contacted with said compound indicates that the compound effects vascularization of allantois. The method used to determine if a compound effects

vasculogenesis is essential for one of skill to determine if a compound effects vasculogenesis and is not in the claim. However, such a step is required in the claim. Please provide support where the specification discusses how to determine whether a compound effects vasculogenesis by page and line number.

Specifically, the specification does not enable one of skill to determine when a test compound has a "detrimental" effect on vasculogenesis. While the term was known in the art, the term is relative. Is a slowing of vasculogenesis "detrimental" even if the animal turns out normally? In some cases an effect may be "beneficial" in one patient but "detrimental" to another such as the formation of blood vessels or blood clotting. See 112/2nd.

Therefore, the specification does not enable "observing vasculogenesis" as broadly claimed.

The claims encompass observing the effect of a test compound that is DNA; however, such methods are not being examined in the newly elected restriction group as they were examined previously in Group V.

Therefore, in view of the lack of guidance in the specification regarding how to observe vasculogenesis, evaluate the effect of a test gene product on vasculogenesis, the breadth of the claims and how to determine whether a test gene product is "detrimental" to vasculogenesis, the state of the art, the examples provided and the breadth of the claims, the ordinary artisan at the time of the instant invention would not have known how to make and/or use the claimed invention as broadly claimed.

2. Claims 14, 17, 19, 20 and 24-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 14 and 24 are indefinite because the metes and bounds of what applicants consider an "isolated allantois culture" cannot be determined. It is unclear if the phrase refers to any proliferating allantoic cells that are removed from an embryo or to cells that are isolated from the allantois and cultured *in vitro*. It is also unclear if a "culture" encompasses cells cultured *in ovo*.

Claims 14, 17, 19, 20 and 24-27 are indefinite because the metes and bounds of the phrase "observing vasculogenesis" cannot be determined. In particular, the metes and bounds of when "vasculogenesis" begins cannot be determined. Applicants state the heart, large blood vessels and the vitelline vasculature are formed by vasculogenesis which is a uniquely embryonic process in which pluripotent mesodermal cells differentiate into angioblasts that subsequently aggregate and assemble in situ into new blood vessels (page 63, line 7). However, the specification and the art at the time of filing does not define when vasculogenesis begins. While applicants definition states vasculogenesis includes differentiation of mesodermal cells into angioblasts, the specification does not define this as the beginning of vasculogenesis. Applicants teach the allantois grows and contacts the chorion prior to becoming the umbilical chord and is essential to form the umbilical chord. It is unclear whether the process of the allantois growing and contacting the chorion is included in "vasculogenesis" of the umbilical chord. Specifically, it is unclear if the phrase

encompasses observing the attachment of transplanted allantois to a chorion (see 102 rejection). Therefore, the metes and bounds of "observing vasculogenesis" cannot be determined.

Claims 17, 19, 20 and 25-27 are indefinite because the metes and bounds of what applicants consider an "cultured allantoic explant" cannot be determined. It is unclear if the phrase refers to proliferating allantoic cells that are removed from an embryo or to cells that are isolated from the allantois and cultured *in vitro*. It is also unclear if a "explant" encompasses cells cultured *in ovo*.

Furthermore, the metes and bounds of what applicants consider "applying a test compound to a cultured allantoic explant" cannot be determined. It is unclear if contacting allantoic cells with a recipient embryo is encompassed by the claim. The recipient embryo could be a "test compound" because the effect of the recipient embryo on the donor allantois is observed. Clarification is required.

Claims 17, 19, 20 and 25-27 are indefinite because the methods are missing at least one essential step - the method used to determine whether a compound effects vasculogenesis. For example, such a step could be: comparing the vascularization of an allantois contacted with a compound to the vascularization of an allantois not contacted with said compound, wherein an alteration in the vascularization of the allantois contacted with said compound as compared to the vascularization of the allantois not contacted with said compound indicates that the compound effects vascularization of allantois.

Claim 26 is indefinite because it appears that the claim is directed toward an assay for determining whether a compound has an effect on blood vessel formation. However, the effect may be positive, negative or may not occur. Therefore, it is unclear the limitation is further describing how to determine if compound has a negative effect on blood vessel formation or is intended to change the claim to a method resulting in inhibiting blood vessel formation in an allantois. In either case, the preamble of the claim and the body of the claim are not commensurate in scope.

The metes and bounds of what is encompassed by determining whether a compound has a "detrimental" effect on vasculogenesis cannot be determined. While the term "detrimental" was known in the art and various methods of determining the effect of a compound on vasculogenesis can be envisioned, it is unclear what effects are considered "detrimental" as claimed. For example, a slowing of vasculogenesis may occur even if the animal turns out normally. Is the slowing down of vasculogenesis "detrimental" if the animal is normal? As another example, some compounds may have an effect that is "beneficial" under some circumstances but "detrimental" in others (e.g. the formation of blood vessels or blood clotting). A phrase such as "wherein the compound inhibits vascularization" "wherein the compound inhibits the allantois from contacting the chorion" would overcome this rejection. Please make sure to provide support for any such limitations add to the claims by page and line number.

Claim Rejections - 35 USC § 102

3. Claims 14, 17, 19, 20 and 24-27 are rejected under 35 U.S.C. 102(b) as being anticipated by Downs (Downs et al., Feb. 1995, Development, Vol. 121, pages 407-416).

Claims 14 and 24 are directed toward preparing an isolated allantois culture and observing vasculogenesis. Downs taught isolating the allantois from embryos and observing the vascularization of the developing embryo (page 411, para. bridging col. 1 and 2). Removing the allantois is equivalent to "preparing an isolated allantois culture" because the allantois is isolated from an embryo and the cells are proliferating.

In addition, Downs taught isolating whole or half allantoises from embryos and transplanting the allantois into a donor embryo (para. bridging pages 408 and 409) which is equivalent to "preparing an isolated allantois culture" because the allantoic tissue is isolated from embryos and the cells are reproducing and because the allantois is cultured in another embryo *in ovo*. The transplanted allantois were observed for attachment to the chorion (page 409, col. 1, first para.). Attachment of the allantois to the chorion is part of vasculogenesis because attachment to the allantois to the chorion is required for the allantois to become vascularized (page 407, col. 2, 5 lines from the bottom) and become the umbilical chord. Therefore, observing attachment of the allantois to the chorion is equivalent to observing vasculogenesis.

Claims 17, 19, 20 and 25-27 are directed toward applying a compound to a cultured allantoic explant and observing the effect of the compound of vasculogenesis. The allantoises of Downs were labeled with [^{3}H]methyl thymidine (page 408, col. 2, para. 3) which is equivalent to

applying a test compound to a cultured allantoic explant as claimed. The allantoises are cultured allantoic explants because they are isolated from embryos and cultured in other embryos. The effect of [^{3}H]methyl thymidine on growth and development was observed (page 409, col. 1, line 14). Observing the growth and development of the allantois is equivalent to observing vasculogenesis because the allantois develops vascular tissue. The limitation of a test compound that has a detrimental effect (claim 26) does not bear patentable weight because the claim is an assay for determining the effect of a compound on vasculogenesis, because the compound may have a positive or negative effect on vasculogenesis or no effect at all, and because the claim is not a method of inhibiting vasculogenesis (see 112/2nd).

In addition, the recipient embryos of Downs are also equivalent to "test compounds." Observing the growth and development of the allantois within the recipient embryo is equivalent to observing vasculogenesis. The donor allantois inherently contacts proteins on or around the recipient embryo transplantation site which is equivalent to applying a "gene product" to a cultured allantoic explant as claimed (claim 27).

Thus, Downs anticipates the claims as written.

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-0120.

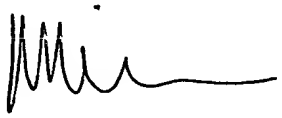
Questions of formal matters can be directed to the patent analyst, Tracey Johnson, who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-2982.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Deborah Clark, can be reached on (703) 305-4051.

The official fax number for this Group is (703) 308-4242.

Michael C. Wilson



MICHAEL C. WILSON
PATENT EXAMINER